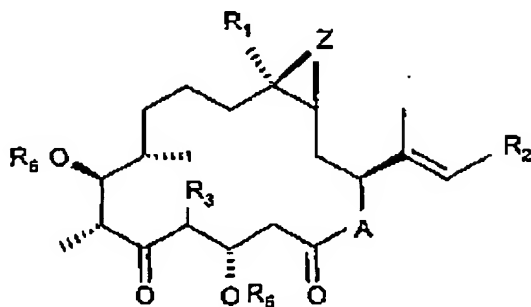


Amendments to the Claims:

JC17 Rec'd PCT/JP 09 JUN 2005

Listing of Claims:

Claim 1 (currently amended): An epothilone of formula I



(I)

wherein

A represents O or NR<sub>7</sub>[[,]];

R<sub>1</sub> is hydrogen or lower alkyl which is unsubstituted or substituted by hydroxy, lower acyloxy, lower alkanoyl in free or protected form, lower alkoxy, halogen, amino, lower alkyl amino, di-lower alkyl amino, or lower acyl amino[[,]];

R<sub>2</sub> is unsubstituted or substituted heteroaryl having at least one nitrogen atom,

R<sub>3</sub> represents hydrogen or lower alkyl[[,]];

R<sub>5</sub> and R<sub>6</sub> are hydrogen, and

R<sub>7</sub> is hydrogen or lower alkyl[[,]];

Z is O or a bond[[,]];

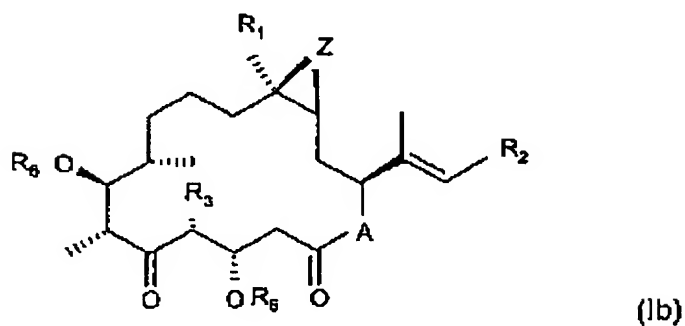
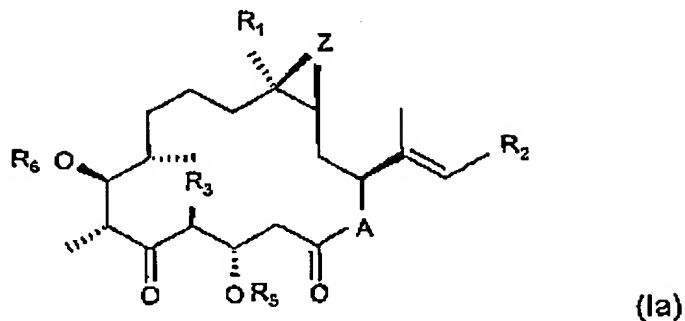
~~under-with~~ the proviso that

when R<sub>2</sub> is 2-methyl-thiazolyl and Z is O, R<sub>1</sub> represents lower alkyl which is unsubstituted or substituted by hydroxy, lower acyloxy, lower alkoxy, halogen, amino, lower alkyl amino, di-lower alkyl amino or lower acyl amino, and

when R<sub>2</sub> is 2-methyl-thiazolyl and Z is a bond, R represents lower alkyl which is substituted by hydroxy, lower acyloxy, lower alkoxy, halogen, amino, lower alkyl amino, di-lower alkyl amino or lower acyl amino,

or a salt thereof.

Claim 2 (currently amended): An epothilone of formula Ia or Ib



wherein

A represents O or NR<sub>7</sub>[[,]];

R<sub>1</sub> is hydrogen or lower alkyl which is unsubstituted or substituted by hydroxy, lower acyloxy, lower alkanoyl in free or protected form, lower alkoxy, halogen, amino, lower alkyl amino, all-lower alkyl amino, or lower acyl amino[[,]];

R<sub>2</sub> is unsubstituted or substituted heteroaryl having at least one nitrogen atom,

R<sub>3</sub> represents hydrogen or lower alkyl[[,]];

R<sub>5</sub> and R<sub>6</sub> are hydrogen, and

R<sub>7</sub> is hydrogen or lower alkyl[[,]];

Z is O or a bond[[,]];

under the proviso that

when R<sub>2</sub> is 2-methyl-thiazolyl and Z is O, R<sub>1</sub> represents lower alkyl which is unsubstituted or substituted by hydroxy, lower acyloxy, lower alkoxy, halogen, amino, lower alkyl amino, di-lower alkyl amino or lower acyl amino[[,]]; and

when R<sub>2</sub> is 2-methyl-thiazolyl and Z is a bond, R<sub>1</sub> represents lower alkyl which is substituted by hydroxy, lower acyloxy, lower alkoxy, halogen, amino, lower alkyl amino, di-lower alkyl amino or lower acyl amino[[,]];

or a salt thereof.

Claim 3 (currently amended): The epothilone of formula I according to claim 1 ~~or of formula Ia or Ib according to claim 2~~, wherein

A represents O or NR<sub>7</sub>[[,]];

R<sub>1</sub> is hydrogen or lower alkyl which is unsubstituted or substituted by hydroxy, lower acyloxy, lower alkanoyl in free or protected form, lower alkoxy, halogen, amino, lower alkyl amino, di-lower alkyl amino, or lower acyl amino[[,]];

R<sub>2</sub> is thiazolyl, oxazolyl, pyridyl, benzothiazolyl, benzoxazolyl or benzoimidazolyl, which in each case is substituted or unsubstituted[[,]];

R<sub>3</sub> represents hydrogen or lower alkyl[[,]];

R<sub>5</sub> and R<sub>6</sub> are hydrogen[[,]]; ~~and~~

R<sub>7</sub> is hydrogen or lower alkyl[[,]];

Z is O or a bond[[,]];

~~under~~ with the proviso that

when R<sub>2</sub> is 2-methyl-thiazolyl and Z is O, R<sub>1</sub> represents lower alkyl which is unsubstituted or substituted by hydroxy, lower acyloxy, lower alkoxy, halogen, amino, lower alkyl amino, di-lower alkyl amino or lower acyl amino[[,]]; and

when R<sub>2</sub> is 2-methyl-thiazolyl and Z is a bond, R<sub>1</sub> represents lower alkyl which is substituted by hydroxy, lower acyloxy, lower alkoxy, halogen, amino, lower alkyl amino, di-lower alkyl amino or lower acyl amino, or a salt thereof.

Claim 4 (currently amended): The epothilone of formula I according to claim 1 ~~or of formula Ia or Ib according to claim 2~~, wherein

A represents O or NR<sub>7</sub>[[,]];

R<sub>1</sub> is hydrogen or lower alkyl which is unsubstituted or substituted by hydroxy, lower acyloxy, lower alkoxy, halogen, amino, lower alkyl amino, di-lower alkyl amino or lower acyl amino[[,]];

R<sub>2</sub> is thiazolyl, oxazolyl, pyridyl, benzothiazolyl, which in each case is substituted or unsubstituted[[,]];

R<sub>3</sub> represents hydrogen or lower alkyl[[,]];

R<sub>5</sub> and R<sub>6</sub> are hydrogen[[,]]; ~~and~~

R<sub>7</sub> is hydrogen or lower alkyl[[,]];

Z is O or a bond[[,]]

~~under~~ with the proviso that

when R<sub>2</sub> is 2-methyl-thiazolyl and Z is O, R<sub>1</sub> represents lower alkyl which is unsubstituted or substituted by hydroxy, lower acyloxy, lower alkoxy, halogen, amino, lower alkyl amino, di-lower alkyl amino or lower acyl amino[[,]]; and

when R<sub>2</sub> is 2-methyl-thiazolyl and Z is a bond, R<sub>1</sub> represents lower alkyl which is substituted by hydroxy, lower acyloxy, lower alkoxy, halogen, amino, lower alkyl amino, di-lower alkyl amino or lower acyl amino[[,]] or a salt thereof.

Claim 5 (currently amended): The epothilone of formula I according to claim 1 ~~or of formula Ia or Ib according to claim 2~~, wherein

A represents O[[,]];

R<sub>1</sub> is hydrogen or lower alkyl[[,]];

R<sub>2</sub> is 2-methyl-thiazolyl, 2-ethyl-thiazolyl, 2-methylthio-thiazolyl, 2-aminomethyl-thiazolyl, 2-dimethylamino-thiazolyl, 2-fluoromethyl-thiazolyl, 2-methyl-oxazolyl, 3-methyl-pyridinyl, 2-methyl- benzothiazolyl[[,]];

R<sub>3</sub> represents hydrogen or lower alkyl[[,]];

R<sub>5</sub> and R<sub>6</sub> are hydrogen[[,]] ~~and~~

Z is O or a bond[[,]];

~~under-with~~ the proviso that when R<sub>2</sub> is 2-methyl-thiazolyl, Z is O and R<sub>1</sub> represents lower alkyl, or a salt thereof.

Claim 6 (currently amended): The epothilone of formula I according to claim 1 ~~or of formula Ia or Ib according to claim 2~~, wherein

A represents O[[,]];

R<sub>1</sub> is hydrogen or lower alkyl[[,]];

R<sub>2</sub> is 2-methyl-thiazolyl, 2-ethyl-thiazolyl, 2-methylthio-thiazolyl, 2-aminomethyl-thiazolyl, 2-dimethylamino-thiazolyl, 2-fluoromethyl-thiazolyl, 2-methyl-oxazolyl, 3-methyl-pyridinyl, 2-methyl-benzothiazolyl[[,]];

R<sub>3</sub> represents methyl[[,]];

R<sub>5</sub> and R<sub>6</sub> are hydrogen[[,]] ~~and~~

Z is O or a bond[[,]];

~~under-with~~ the proviso that when R<sub>2</sub> is 2-methyl-thiazolyl, Z is O and R<sub>1</sub> represents lower alkyl, or a salt thereof.

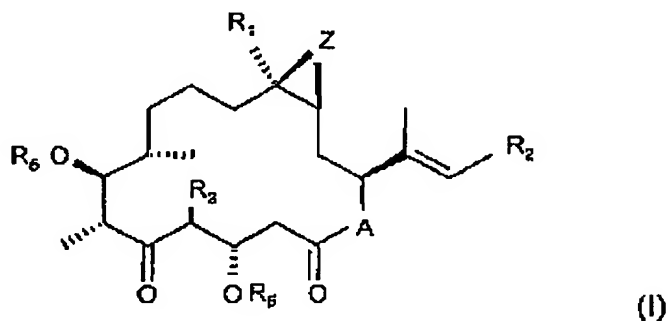
Claim 7 (currently amended): A pharmaceutical composition, comprising an epothilone of formula I ~~or of formula Ia or Ib~~ according to claim 1, or a pharmaceutically acceptable salt

thereof, provided that salt-forming groups are present, ~~according to one of claims 1 to 6,~~  
and one or more pharmaceutically acceptable carriers.

Claims 8-9 (canceled)

Claim 10 (currently amended): A method for treatment of warm-blooded animals, including humans, in which an therapeutically effective amount of an epothilone of the formula I ~~or of formula Ia or Ib~~ according to ~~any one of claims 1 to 6~~ claim 1 or a pharmaceutically acceptable salt of such a compound is administered to a warm-blooded animal suffering from a tumour disease.

Claim 11 (currently amended): A process for the preparation of an epothilone of formula I,



wherein

A represents O or NR<sub>7</sub>[[,]];

R<sub>1</sub> is hydrogen or lower alkyl which is unsubstituted or substituted by hydroxy, lower acyloxy, lower alkoxy, halogen, amino, lower alkyl amino, di-lower alkyl amino or lower acyl amino[[,]];

R<sub>2</sub> is unsubstituted or substituted heteroaryl having at least one nitrogen atom[[,]];

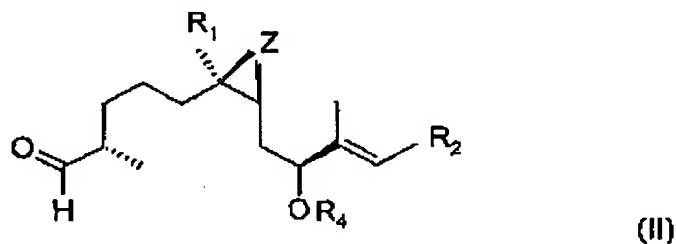
R<sub>3</sub> represents hydrogen or lower alkyl[[,]]; and

R<sub>5</sub> and R<sub>6</sub> are hydrogen[[,]]; and

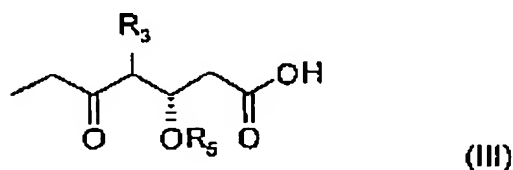
R<sub>7</sub> is hydrogen or lower alkyl[[,]]; and

Z is O or a bond[[,]]; or a pharmaceutically acceptable salt thereof; comprising the steps of:

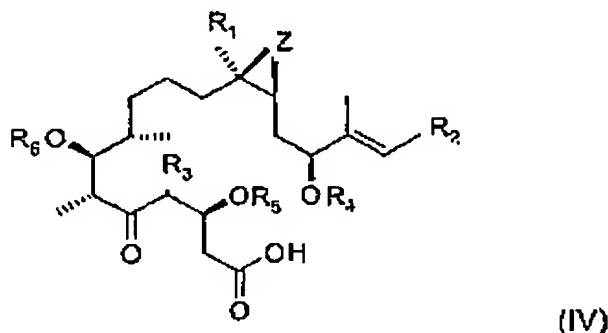
(a) reacting wherein an aldehyde of formula II



wherein R<sub>1</sub>, R<sub>2</sub> and Z have the meanings as provided above for a compound of formula I and  
R<sub>4</sub> is a protecting group, ~~is reacted in a first step with an ethylketone of formula III,~~



wherein R<sub>5</sub> is H or a protecting group different or identical to R<sub>4</sub> and R<sub>3</sub> has the meaning as  
provided above for a compound of formula I, to provide the aldol of formula IV,



wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and Z have the meanings as provided above for a compound of formula I,  
R<sub>4</sub> a protecting group, R<sub>5</sub> is H or a protecting group different or identical to R<sub>4</sub> and R<sub>6</sub> is  
hydrogen[[,]]

~~which (b) reacting the aldol of formula IV is reacted in a second step with a reagent capable to~~  
introduce a protecting group which is different or identical to R<sub>4</sub> furnishing a carboxylic  
acid of formula IV,

wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and Z have the meanings as provided above for a compound of formula I,  
R<sub>4</sub> a protecting group and R<sub>5</sub> is H or R<sub>5</sub> and R<sub>6</sub> are protecting groups different or identical  
to R<sub>4</sub>[[,]];

~~which (c) reacting the carboxylic acid of formula IV is reacted in a third step with a reagent~~  
capable to remove the protecting group R<sub>4</sub> under conditions which do not result in the  
removal of the protecting groups R<sub>5</sub> and R<sub>6</sub> providing a carboxylic acid of formula IV,

wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and Z have the meanings as provided above for a compound of formula I,  
R<sub>4</sub> is hydrogen and R<sub>5</sub> is H or R<sub>5</sub> is H or R<sub>5</sub> and R<sub>6</sub> are protecting groups,

~~which (d) macrolactonizing the carboxylic acid of formula IV in a fourth step is subject of a~~  
macrolactonisation reaction providing the epothilone of formula I,

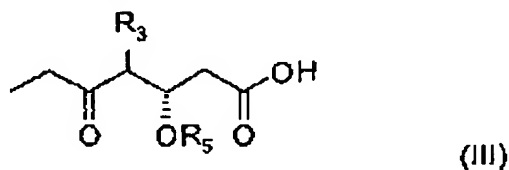
wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and Z have the meanings as provided above for a compound of formula I,  
A is O and R<sub>5</sub> is H or R<sub>5</sub> and R<sub>6</sub> are protecting groups[[,]];

~~which (e) reacting the epothilone of formula I is reacted in a fifth step with a reagent capable to remove of removing the protecting groups R<sub>5</sub> and R<sub>6</sub> furnishing an epothilone of formula I,~~

wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, R<sub>6</sub> and Z have the meanings as provided above for a compound of formula I and A is O[[,]]; and

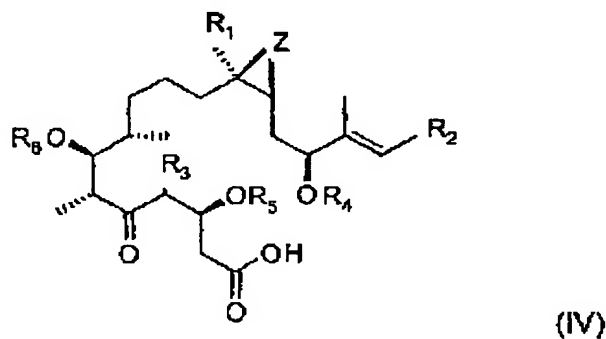
~~which (f) optionally reacting the epothilone of formula I is, optionally, further transformed into an epothilone of formula I wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, R<sub>6</sub> and Z have the meanings as provided above for a compound of formula I and A is NR<sub>7</sub>, wherein R<sub>7</sub> is hydrogen or lower alkyl.~~

Claim 12 (original): An ethylketone of formula III,



wherein R<sub>3</sub> has the meaning as provided above for a compound of formula I and R<sub>5</sub> is hydrogen or a protecting group.

Claim 13 (currently amended): An aldol of formula IV,



R<sub>1</sub> is hydrogen or lower alkyl which is unsubstituted or substituted by hydroxy, lower acyloxy,

lower alkoxy, halogen, amino, lower alkyl amino, di-lower alkyl amino, lower acyl amino,

R<sub>2</sub> is unsubstituted or substituted heteroaryl[[,]];

R<sub>3</sub> represents hydrogen or lower alkyl[[,]];

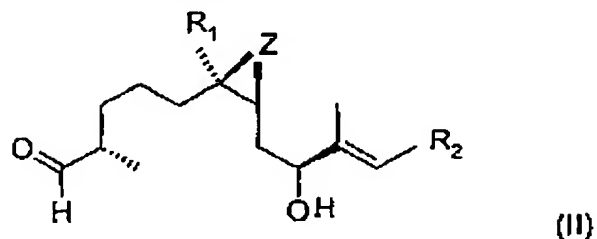
R<sub>4</sub> is hydrogen or a protecting group[[,]];

R<sub>5</sub> is a protecting group different or identical to R<sub>4</sub>[[,]];

R<sub>6</sub> is hydrogen or a protecting group different or identical to R<sub>4</sub>[[,]]; and

Z is O or a bond.

Claim 14 (currently amended): A process for the preparation of an aldehyde of formula II



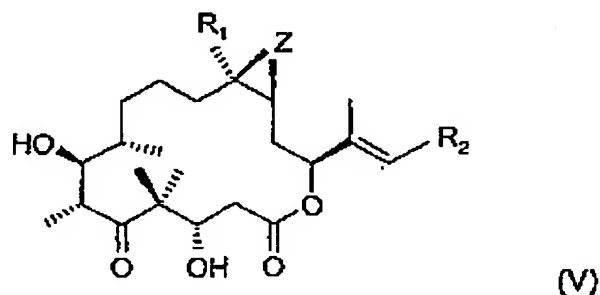
wherein

R<sub>1</sub> is hydrogen or lower alkyl which is unsubstituted or substituted by hydroxy, lower acyloxy, lower alkoxy, halogen, amino, lower alkyl amino, di-lower alkyl amino, lower acyl amino[,,];

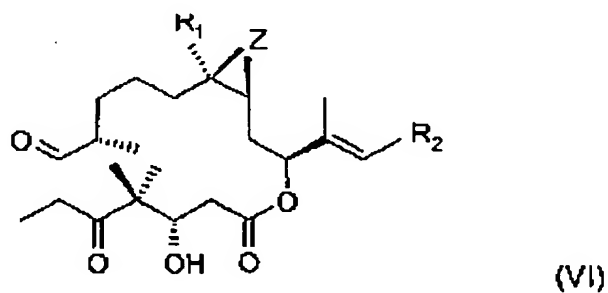
R<sub>2</sub> is unsubstituted or substituted heteroaryl[,,];

Z is O or a bond[,,]; comprising the steps of:

wherein (a) reacting an epothilone of formula V



wherein the radicals R<sub>1</sub>, R<sub>2</sub> and Z have the meanings as provided for a compound of formula II above, ~~is first reacted~~ with a reagent effecting a retro-aldol reaction furnishing an ester of formula VI



wherein the radicals R<sub>1</sub>, R<sub>2</sub> and Z have the meanings as provided for a compound of formula II above, which ester is hydrolyzed in a second step into its components, 4,4-dimethyl-3-hydroxy-5 oxo-heptanoic acid and the aldehyde of formula II as defined above.



Claim 15 (original): A method of separating C4-desmethyl-epothilone B from epothilone G2, which is characterized by chromatography on a Chiralpak-AD column with an eluant containing a lower alkane and a lower alkanol.

Claim 16 (original): A process for the production of C4-desmethyl-epothilone B, which comprises the steps of

- a) concentrating epothilones in a culture medium for the biotechnological preparation of epothilones, which medium contains a microorganism suitable for the preparation of epothilones, water and other suitable customary constituents of culture media, whereby a cyclodextrin or a cyclodextrin derivative is added to the medium, or a mixture of two or more of these compounds;
- b) separating epothilones from one another, which is characterized by chromatography on a reversed-phase column with an eluant containing a lower alkylcyanide, wherein chromatography is carried out on column material charged with hydrocarbon chains, and an eluant containing a lower alkylnitrile is used; and wherein, if desired, further working up steps and purification steps are possible; and
- c) finally separating C4-desmethyl-epothilone B from epothilone G2, by chromatography on a Chiralpak-AD column with an eluant containing a lower alkane, and a lower alkanol.

Claim 17 (new): The epothilone of formula Ia or Ib according to claim 2, wherein A represents O or NR<sub>7</sub>;

R<sub>1</sub> is hydrogen or lower alkyl which is unsubstituted or substituted by hydroxy, lower acyloxy, lower alkanoyl in free or protected form, lower alkoxy, halogen, amino, lower alkyl amino, di-lower alkyl amino, or lower acyl amino;

R<sub>2</sub> is thiazolyl, oxazolyl, pyridyl, benzothiazolyl, benzoxazolyl or benzoimidazolyl, which in each case is substituted or unsubstituted;

R<sub>3</sub> represents hydrogen or lower alkyl;

R<sub>5</sub> and R<sub>6</sub> are hydrogen;

R<sub>7</sub> is hydrogen or lower alkyl;

Z is O or a bond;

with the proviso that

when R<sub>2</sub> is 2-methyl-thiazolyl and Z is O, R<sub>1</sub> represents lower alkyl which is unsubstituted or substituted by hydroxy, lower acyloxy, lower alkoxy, halogen, amino, lower alkyl amino, di-lower alkyl amino or lower acyl amino; and

when R<sub>2</sub> is 2-methyl-thiazolyl and Z is a bond, R<sub>1</sub> represents lower alkyl which is substituted by hydroxy, lower acyloxy, lower alkoxy, halogen, amino, lower alkyl amino, di-lower alkyl amino or lower acyl amino, or a salt thereof.

Claim 18 (new): The epothilone of formula Ia or Ib according to claim 2, wherein

A represents O or NR<sub>7</sub>;

R<sub>1</sub> is hydrogen or lower alkyl which is unsubstituted or substituted by hydroxy, lower acyloxy, lower alkoxy, halogen, amino, lower alkyl amino, di-lower alkyl amino or lower acyl amino;

R<sub>2</sub> is thiazolyl, oxazolyl, pyridyl, benzothiazolyl, which in each case is substituted or unsubstituted;

R<sub>3</sub> represents hydrogen or lower alkyl;

R<sub>5</sub> and R<sub>6</sub> are hydrogen;

R<sub>7</sub> is hydrogen or lower alkyl;

Z is O or a bond;

with the proviso that

when R<sub>2</sub> is 2-methyl-thiazolyl and Z is O, R<sub>1</sub> represents lower alkyl which is unsubstituted or substituted by hydroxy, lower acyloxy, lower alkoxy, halogen, amino, lower alkyl amino, di-lower alkyl amino or lower acyl amino; and

when R<sub>2</sub> is 2-methyl-thiazolyl and Z is a bond, R<sub>1</sub> represents lower alkyl which is substituted by hydroxy, lower acyloxy, lower alkoxy, halogen, amino, lower alkyl amino, di-lower alkyl amino or lower acyl amino or a salt thereof.

Claim 19 (new): The epothilone of formula Ia or Ib according to claim 2, wherein

A represents O;

R<sub>1</sub> is hydrogen or lower alkyl;

R<sub>2</sub> is 2-methyl-thiazolyl, 2-ethyl-thiazolyl, 2-methylthio-thiazolyl, 2-aminomethyl-thiazolyl, 2-dimethylamino-thiazolyl, 2-fluoromethyl-thiazolyl, 2-methyl-oxazolyl, 3-methyl-pyridinyl, 2-methyl- benzothiazolyl;

R<sub>3</sub> represents hydrogen or lower alkyl;

R<sub>5</sub> and R<sub>6</sub> are hydrogen;

Z is O or a bond;

with the proviso that when R<sub>2</sub> is 2-methyl-thiazolyl, Z is O and R<sub>1</sub> represents lower alkyl, or a salt thereof.

Claim 20 (new): The epothilone of formula Ia or Ib according to claim 2, wherein

A represents O;

R<sub>1</sub> is hydrogen or lower alkyl;

R<sub>2</sub> is 2-methyl-thiazolyl, 2-ethyl-thiazolyl, 2-methylthio-thiazolyl, 2-aminomethyl-thiazolyl, 2-dimethylamino-thiazolyl, 2-fluoromethyl-thiazolyl, 2-methyl-oxazolyl, 3-methyl-pyridinyl, 2-methyl-benzothiazolyl;

R<sub>3</sub> represents methyl;

R<sub>5</sub> and R<sub>6</sub> are hydrogen;

Z is O or a bond;

with the proviso that when R<sub>2</sub> is 2-methyl-thiazolyl, Z is O and R<sub>1</sub> represents lower alkyl, or a salt thereof.

Claim 21 (new): A pharmaceutical composition, comprising an epothilone of formula Ia or Ib according to claim 2, or a pharmaceutically acceptable salt thereof, provided that salt-forming groups are present, one or more pharmaceutically acceptable carriers.

Claim 22 (new): A method for treatment of warm-blooded animals, including humans, in which an therapeutically effective amount of an epothilone of the formula Ia or Ib according to claim 2 or a pharmaceutically acceptable salt of such a compound is administered to a warm-blooded animal suffering from a tumour disease.